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de Lange Syndrome: Report of 20 Cases

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Typus Degenerativus Amstelodamensis or Amsterdam dwarfism, a syndrome of unknown etiology characterized by mental retardation, a distinctive face, characteristic hands and feet, defective growth and other minor malformations, was first described by Cornelia de Lange in 1933. Approximately 69 cases, including nine autopsies, have been reported in the literature. In this paper we present a further 20, with illustrations of the syndrome from infancy to puberty (including de Lange's original three cases). The historical, physical, laboratory and radiographic findings of de Lange's three patients and our 20 are tabulated. Autopsy findings in one of our patients are reported and the literature is briefly reviewed.

Although some observers have recently reported chromosome abnormalities in de Lange's syndrome, we feel that the diagnosis is made from the history and physical examination and that there are no definitive laboratory aids which can confirm the diagnosis. Chromosome studies in all 20 of our patients were normal and the genetic implications are discussed.

Typus Degenerativus Amstelodamensis ou nanisme du type d'Amsterdam, syndrome d'étiologie inconnue qui se caractérise par de l'arriération mentale, un faciès typique, des mains et des pieds également caractéristiques, des troubles de croissance et d'autres malformations mineures, a été décrit pour la première fois par Cornelia de Lange en 1933. On trouve près de 69 cas rapportés dans la littérature, dont neuf autopsies. Dans le présent article, nous présentons 20 nouveaux cas, avec illustrations du syndrome de la première enfance à la puberté (notre étude comporte les trois cas originaux de de Lange). Les observations historiques et les protocoles radiologiques des trois cas de de Lange et de nos 20 cas personnels sont présentés sous forme de tableaux. Nous donnons le protocole d'autopsie d'un de nos cas. La littérature est brièvement passée en revue.

Même si certains observateurs ont récemment signalé des anomalies chromosomiques dans le syndrome de de Lange, nous estimons que le diagnostic est basé sur l'histoire clinique et l'examen somatique et croyons qu'il n'existe pas d'épreuve de laboratoire valable, susceptible de confirmer le diagnostic. Dans nos 20 cas, les cariotypes chromosomiques étaient tous normaux. L'article soulève la possibilité d'implications génétiques.

Cornelia de Lange‡ was born in Alkmaar, Holland, in 1871 and died in 1950. She graduated from medical school in Amsterdam in 1897 and worked as a general practitioner before specializing in pediatrics and the pathology of the neonatal brain, on which she wrote many papers. In 1927 she became Professor of Pediatrics at the University of Amsterdam and in 1939 returned to the Emma Children's Hospital. Not only did de Lange define, in a description of two cases,[1] Typus Degenerativus Amstelodamensis (naming it after the city in which she worked), but five years later (1938) reported the autopsy findings of her first case, and described clinically a third case.[2] Her writing was mainly in Dutch but occasionally in French, as were her two papers describing this syndrome.

Cornelia de Lange was the pioneer of the diagnosis of pyuria in young children, about which she wrote in 1903. She also published numerous papers about abdominal disorders, blood diseases and tuberculosis and also many case reports. At 78 years of age she made a major contribution in a paper on "The traumatic changes in the brain of fully developed children after spontaneous birth". She was President of the Dutch Pediatric Society for many years, and was created a Knight of the Order of the Dutch Lion. In addition to being distinguished as a clinician and neuropathologist, she was an accomplished classical scholar.

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HISTORICAL REVIEW

IN 1916 Brachmann[9] described a syndrome of dwarfism, cervical ribs and hypertrichosis following a detailed dissection of the bones and muscles of a neonate (Fig. 1) who also had bilateral monodactyly from an ulnar defect and symmetrical webbing of the elbows. Unfortunately, as the specimen had been preserved in alcohol after evisceration, and the fixation of the brain was unsatisfactory, the pathological study was rather limited. The gestation was normal and birth was at term (birth weight: 1600 g.); this degree of fetal growth retardation has been described in de Lange syndrome (de Lange's first patient weighed 1.2 kg. at term) but is not an invariable feature. The photograph does not look altogether typical of de Lange syndrome; the fleshy and wrinkled appearance, the large ears and the short neck suggesting some distinct syndrome. The urethral opening could not be found in the malformed penis, and this suggests the possibility of Potter's syndrome superimposed on an abnormality of both arms.

In view of the limited data available from this brief pathological report on an eviscerated infant, we do not consider it useful to confuse the nomenclature by speaking of either Brachmann's syndrome or the Brachmann/de Lange syndrome.

If the eponym "Brachmann's" is used, we suggest it be restricted to cases resembling his case, with severe bilateral arm defects. This may be a very severe manifestation of de Lange syndrome, or a distinct entity. In our case with similar skeletal defects the face was very typical and the diagnosis obvious (Case 1, Fig. 2).

Cornelia de Lange[1] described in 1933 the condition in two infant girls from Amsterdam under the name Typus Degenerativus Amstelodamensis. The terms "de Lange syndrome" and "Amsterdam dwarf" are in common use, and in our opinion the clinical recognition of this syndrome justifies the eponym which has the unusual advantages of brevity and distinctiveness. The abbreviation "Amsterdam dwarf" is not always accurate, as dwarfism is not invariable.

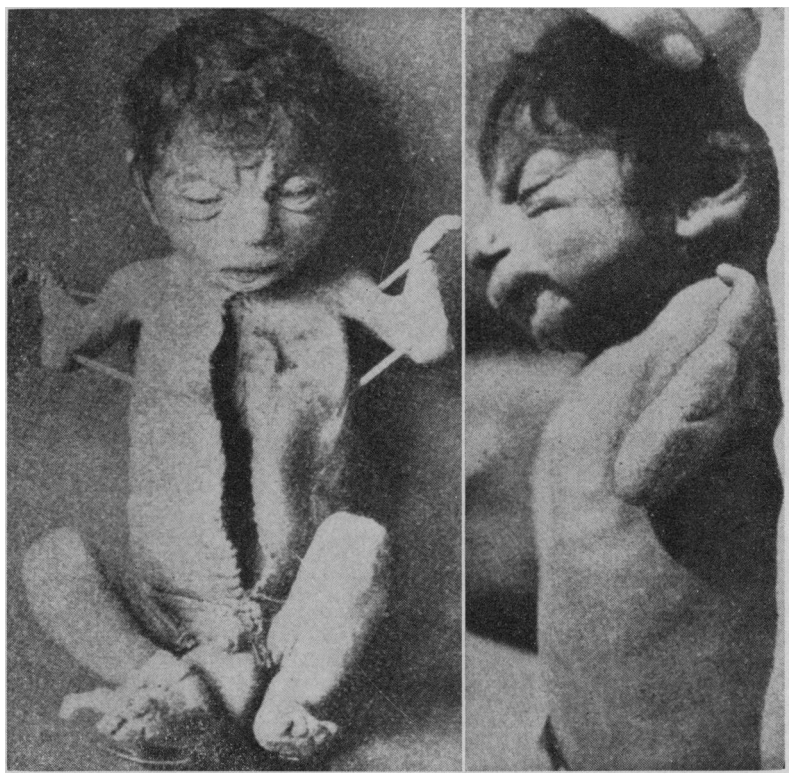


Fig. 1.—Brachmann's case (1916).

Details of her three cases are tabulated in Tables I to IV; the salient features of this syndrome were given by de Lange in the following literal translation. The French text is given in the appendix.

"Now, which are the essential features of this combined degeneration (multiple Abartung) and

TABLE I.—FEATURES IN THREE CASES OF TYPUS DEGENERATIVUS AMSTELODAMENSIS REPORTED BY DE LANGE FROM AMSTERDAM AND IN 20 CASES REPORTED FROM BIRMINGHAM

Subject	Age at time of investigation (years)	Sex	Gestation (weeks)	Birth weight (Kg.)	Birth length (cm.)	Parental age (years)		Significant family illnesses	Normal pregnancy	Normal delivery	Cyanosed at birth	Delayed milestones	Delayed eruption of teeth	Retarted growth	Vomiting as a major symptom in first two years of life	Recurrent chest infection	Other problems
						Mother	Father										
A1	1 6/12	F	40	1.25				—				+	+	+	+	+	Died at age 5 years 9 mths.
A2	6/12	F	40	2.0	45			—				+	+	+		+	Died.
A3	11/12	F	40	1.75				—				+		+			Incubator (4 months) "Stridulous" cry. Died at age 11½ months.
1	4/12	M	36	1.5		20	22	—	+	+	+	+	+	+	+	+	
2	9/12	M	35	.95	35.6	24	28	—	+	breech	+	+	+	+	+	+	Died (pneumonia).
3	1 6/12	M	41	3.9		36	35	—	+	+	+	+	+	+	—	+	
4	1 9/12	F	38	1.5	38.1	21	23	—	+	+	+	+	+	+	+	+	Died (pneumonia).
5	2	F	37	1.6	40.6	24	28	—	+	+	+	+	+	+	+	+	Died (convulsions).
6	2 1/12	M	38	2.3		44	42	—	—	+	—	+	+	+	+	+	
7	2 9/12	M	40	2.8				—	+	+	—	+	+	+	+	+	
8	2 11/12	M	41	3.1		24	28	—	—	+	—	+	+	+	—	—	Hemolytic diseases of the newborn.
9	3 6/12	M	38	3.1		30	30	—	+	+	—	+	+	+	—	+	Chronic urinary infection.
10	4 9/12	M	39	3.6		28	30	—	+	+	—	+	+	—	+	—	
11	5 1/12	F	40	3.4		26	25	—	+	+	+	+	+	—	+	+	Chronic urinary infection. Photophobia.
12	5 7/12	M	40	3.7		34	33	—	+	+	—	+	+	+	+	+	
13	8 5/12	F	38	2.3		25	24	—	+	+	—	+	+	+	+	+	Photophobia.
14	8 11/12	M	40	2.8		32	33	—	+	+	+	+	+	+	+	+	Photophobia.
15	9 1/12	F	36	1.9		31	30	—	+	+	+	+	+	+	—	—	
16	10 2/12	F	40	2.3		23	31	—	+	+	—	+	+	+	+	+	
17	10 5/12	F	40	3.5		23	26	—	+	+	+	+	+	—	+	—	
18	11 6/12	M	40	3.4		27	29	—	+	+	—	+	+	+	+	+	Convulsions.
19	14 6/12	F	40	3.4		39	41	—	+	+	+	+	+	—	+	+	Convulsions. Enuresis.
20	18 6/12	F	40	2.9		26	28	—	+	+	+	+	+	+	+	+	Enuresis.

A1, A2 and A3 represent W.G., P. de G. and G.P., the three cases described by de Lange.

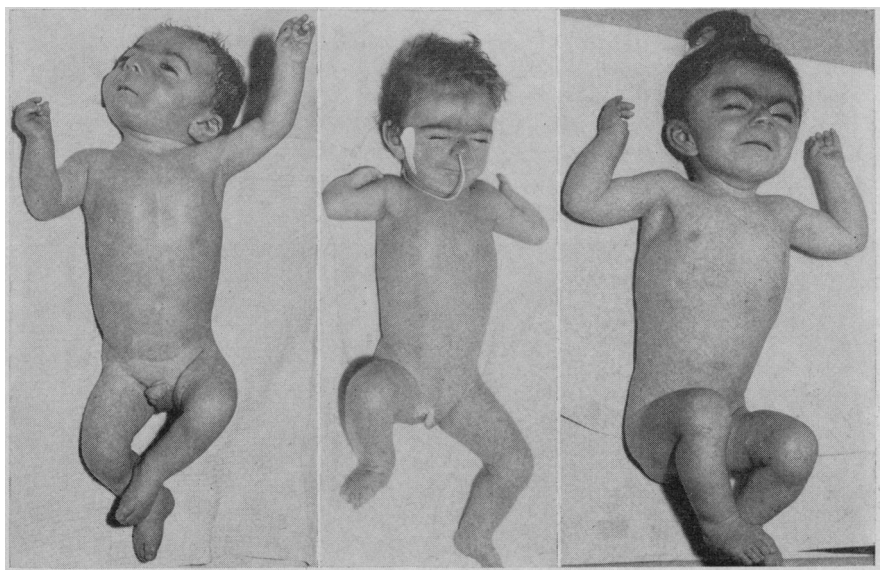


Fig. 2.—Appearance in infancy (from left to right): Case 2, aged 4 months; Case 1, aged 4 months, and Case 6, aged 9 months.

TABLE II.—BODY MEASUREMENTS, MENTAL DEVELOPMENT, HAIR AND FACIAL CHARACTERISTICS IN THREE CASES OF TYPUS DEGENERATIVUS AMSTELODAMENSIS REPORTED BY DE LANGE FROM AMSTERDAM AND IN 20 CASES REPORTED FROM BIRMINGHAM

Subject	Sex	Age (years)	Height		Weight		Head circumference (cm.)	Mental retardation	Hair colour*	Hypertrichosis	Low hairline (forehead)	Prominent eyebrows	Long, curved eyelashes	Narrow palpebral fissure	Short, upturned nose with flat bridge	Elongated philtrum	Receding chin	Thin upper lip	"Carp" mouth
			cm.	Percentile	Kg.	Percentile													
A1	F	1 6/12	65	< 3	5.5	< 3	41	+	D	+	+	+	+		+	+	+		
A2	F	6/12	55	< 3	3.49	+ 3	37	+	D	+	+	+	+		+	+	+	+	+
A3	F	11/12	59	< 3	4.39	< 3	39	+	A	+	+	+	+		+	+	+	+	+
1	M	4/12	53	< 3	2.8	< 3	32.6	+	E	+	+	+	+	+	+	+	+	+	+
2	M	9/12	46	< 3	2.8	< 3	32.4	+	E	+	+	+	+	+	+	+	+	+	+
3	M	1 6/12	73.5	< 3	10	10	48	+	B	+	+	—	+	+	+	+	+	+	+
4	F	1 9/12	50.5	< 3	3.6	< 3	32.8	+	D	+	+	+	+	+	+	+	+	+	+
5	F	2	58	< 3	5.4	< 3	35	+	E	+	+	+	+	+	+	+	+	+	+
6	M	2 1/12	71	< 3	6.4	< 3	40.6	+	E	+	+	+	+	+	+	+	+	+	+
7	M	2 9/12	77.2	< 3	9.5	< 3		+	B	+	+	+	+	+	+	+	+	+	+
8	M	2 11/12	85.5	< 3	12.4	10	49	+	E	+	+	+	+	—	+	+	+	+	+
9	M	3 6/12	81.5	< 3	11.3	< 3	45	+	A	+	+	+	+	+	+	+	+	+	+
10	M	4 4/12	106	75	19.5	90	51	+	B	—	—	—	+	—	+	+	—	+	+
11	F	5 1/12	103	10	18.5	50	50.7	+	E	+	—	+	+	+	+	+	+	+	+
12	M	5 7/12	102.5	3	17.6	10	48	+	C	+	+	—	—	+	—	—	+	+	+
13	F	8 5/12	112	< 3	23	25	48	+	C	+	+	+	+	+	+	+	+	+	—
14	M	8 11/12	116.5	< 3	20	< 3	45	+	C	+	+	+	+	+	+	+	+	+	+
15	F	9 1/12	116.5	< 3	21.5	< 3	48	+	D	+	+	+	+	+	+	+	+	+	+
16	F	10 2/12	129	10-25	27.5	10-25	50.5	+	E	—	+	+	—	+	+	+	+	+	—
17	F	10 5/12	121	3-10	26	50	48.7	+	D	+	+	+	+	+	+	+	+	+	+
18	M	11 6/12	130	3	26	3	51	+	C	—	+	+	+	+	+	+	+	+	+
19	F	14 6/12	148	3-10	58.5	90	48	+	D	+	+	+	+	+	+	+	+	+	+
20	F	18 6/12	151	< 3	41.5	< 3	49	+	D	+	+	+	+	+	+	+	+	+	+

A1, A2 and A3 represent W.G., P. de G. and G.P., the three cases described by de Lange.
*The following letters represent hair colour: A =blond; B = fair; C = brown; D = dark brown; E = black; R = red.

which are the accidental features? To form an opinion on this question it would be necessary to examine a much greater number of cases. However, it seems probable to me that the mental debility, under developed state (full-term birth with low weight which continues to be below average) brachycephaly, hypertrophy of brows and lashes, small size of hands and feet, close positioning of thumb and thenar eminence, low set ears, and syndactylism of the toes are essential signs. The hirsute forehead, ogival palatal arch, hooked little finger and also the humeral micromelia are possibly accidental symptoms. The syndactylism evidently does not always affect the toes."

Typus Degenerativus Amstelodamensis of de Lange, now usually known as de Lange syndrome or Amsterdam dwarfism, is a syndrome

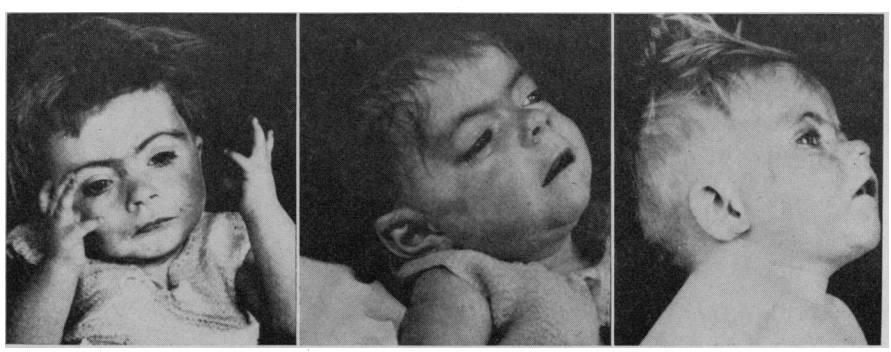


Fig. 3.—de Lange's three patients (from left to right): W.G. (1933), P.deG. (1933) and G.P. (1938), A1, A2 and A3 in our tables.

TABLE III.—SHOWING FEATURES OF HANDS, FEET AND OTHER SIGNS IN THREE CASES OF TYPUS DEGENERATIVUS AMSTELODAMENSIS REPORTED BY DE LANGE FROM AMSTERDAM, AND IN 20 CASES REPORTED FROM BIRMINGHAM

Subject	*Sex*	*Short, tapering fingers*	*Proximally placed thumb*	*Short incurved little finger*	*Small feet and short toes*	*Syndactyly of 2 and 3 toes*	*Joint abnormalities*	*Low-set ears*	*Short neck*	*Skull abnormally shaped*	*Small, widely spaced teeth*	*Cutis marmorata*	*Funnel chest*	*Undescended testes in males*	*Other signs*
A1	F	+	+	+	+	+*		+		+					**Bluish tinge about eyes, nose and mouth. Rickets. High arched palate. Small thenar eminence.
A2	F	+	+		+	+		+		+					Bluish tinge about eyes, nose and mouth. Rickets. High-arched palate. Short forearms. Small thenar eminence.
A3	F	+	+	+	+	+	+	+							Bluish tinge about eyes, nose and mouth. Single transverse palmar crease. Short forearms. thenar eminence. "Contraction of elbows".
1	M				—	—	+	+	+	+		+	—	+	Phocomelia. Oligodactyly. V.S.D. Cleft palate.
2	M	+	+	+	+	+	—	+	+	+		+	+	+	Cleft palate. Webbing of fingers. Hypospadias.
3	M	+	+	+	+	—	—	+	+	+	+	—	—	+	Strabismus.
4	F	+	+	+	+	+	+	+	+	+	+	+	—		Pyloric stenosis.
5	F	+	+	+	+	+	—	+	+	+	+	+	—		
6	M	+	+	+	+	—	+	+	+	+	—	+	+	+	Hypospadias. V.S.D.
7	M	+	+	+	+	—	+	+	+	—	+	—	—	—	Myopia. Strabismus. Nystagmus. Bilateral calcaneo-valgus. Inguinal hernia.
8	M	+	+	—	+	+	—	+	+	—	—	—	—	—	
9	M	+	+	+	+	—	+	+	+	+	+	—	—	+	Cleft palate.
10	M	+	+	+	+	+	—	—	—	—	+	—	+	—	
11	F	+	+	+	+	—	+	+	+	—	—	—	—	—	Myopia. Ptosis of left eyelid. Bilateral coloboma. Cleft palate. Strabismus. V.S.D. Arthrogryposis.
12	M	+	+	+	+	—	—	+	+	+	+	—	—	+	Strabismus.
13	F	+	+	—	+	—	—	+	+	—	—	—	—		
14	M	+	+	—	—	—	+	+	+	—	—	+	+	+	
15	F	+	+	+	+	—	+	+	+	—	—	—	+		Strabismus.
16	F	+	+	+	—	+	—	+	+	—	—	+	+		Inguinal hernia. V.S.D. Myopia. Strabismus. Scoliosis.
17	F	+	+	+	+	+	—	+	+	—	—	+	—		
18	M	+	+	+	+	—	+	+	+	+	+	—	+	+	Strabismus. Ptosis of left eyelid. Arthrogryposis.
19	F	+	+	+	+	—	—	—	+	+	—	+	—		Strabismus. Hemiatrophy. Kyphoscoliosis. Curved middle fingers.
20	F	+	+	+	+	—	+	—	+	—	—	+	+		Hemiatrophy. Spina bifida occulta. Scoliosis.

A1, A2 and A3 represent W.G., P. de G., and G.P., the three cases described by de Lange.
*Syndactyly was present between the 2nd and 3rd toes of the right foot but between the 1st and 2nd toes of the left foot.
**Superficial network of veins. These were prominent in the majority of the infants but not so evident in the older patients.

of unknown etiology characterized by mental retardation, a distinctive face (Fig. 3), characteristic hands and feet, defective growth, and a constellation of minor malformations, none of which is diagnostic. There is usually a history of normal pregnancy, although feeble fetal movements have been noted in several cases. Cyanosis and attacks of apnea are often present immediately after delivery; difficult feeding, persistent vomiting and recurrent infection are common.

The face is characteristic, the distinguishing features being a low hairline, prominent eyebrows which meet in the midline, long curved eyelashes, uptilting nose with upturned nostrils, flat nose bridge, narrow palpebral fissures, epicanthic folds, elongated philtrum, thin upper lip, carp-like mouth and a receding chin. A bluish hue is often noted about the eyes, nose and mouth; temporal and scalp veins may be conspicuous. Children thus affected may have a high arched or cleft palate; the teeth, which

TABLE IV.—LABORATORY AND X-RAY FINDINGS IN THREE CASES OF TYPUS DEGENERATIVUS AMSTELODAMENSIS REPORTED BY de LANGE FROM AMSTERDAM AND IN 20 CASES REPORTED FROM BIRMINGHAM

Subject	Normal chromosomes	Normal urine amino acids	P.B.I. (μg./100 ml.)	Cholesterol (mg. %)	Blood urea (mg. %)	Normal electrolytes	Ca (mg. %)	Pi (mg. %)	Fasting blood sugar (mg. %)	Abnormal E.E.G.	I.Q.	Abnormal E.C.G.	Findings on other investigations	X-ray abnormalities
A1													Hypochromic anemia Wassermann negative Some albuminuria	Hypoplasia of 2nd and 3rd phalanges of little finger. Short first metacarpal.
A2							9.0	3.0					Anisocytosis Poikilocytosis Wassermann negative	Radiographs of the hands not so revealing as in A1.
A3													Blood count normal Some albuminuria	Hypoplasia of 2nd and 3rd phalanges of little finger. Short phalanges and metacarpals. Heavy thick appearance of the diaphysis of the radius and cuboid. Irregularity in ossification. Skull radiograph normal.
1	+													
2	+						11.2	4.8					Normal C.S.F. (lumbar puncture)	Deformity of ribs and clavicles. Bone age retarded. Abnormality of swallowing (lipiodol). Chest, legs, arms normal. Hands and feet not radiographed.
3	+												Normal growth hormone levels	
4	+				33	+								
5	+													
6	+										20			
7	+	+	3.4	156	36		10.2	4.6		N.				Poorly formed left acetabulum. Subluxated left hip. Bone age retarded.
8	+													
9	+	+		266	57		10.5	5.6					Alkaline phosphatase: 23 K.A. units	
10	+										62			Soft tissue syndactyly of 2nd and 3rd digits (both feet). Minor variation in shape of lower ends of ulnae. Ossification consistent with age.
11	+				114							+		Congenital dislocation of left hip. Bilateral subluxation of ankle joints. Bowed fibulae.
12	+				30	+	10.2	4.4						Bilateral dislocation of radial head. Bilateral dislocation of metacarpal phalangeal joints. Thumbs dislocated at distal m.p. joint.
13	+								64					
14	+	+		132	25	+	10.5	6.4	100		40		Alkaline phosphatase: 26 K.A. units	
15	+	+	6.8	122	13	+					65		Normal growth hormone levels	
16	+	+	4.5	226	63		10.7		57		65	+		Bone age consistent with chronological age. Thoraco-lumbar scoliosis. Minor congenital anomaly of little fingers (middle phalanx). Spina bifid (L5S1). No cardiac enlargements.
17	+		6.6	204	39	+	9.7			+			Normal serum lipoproteins	Bone age normal 10 5/12 yr. Six lumbar vert. Unusual modelling at elbow bilaterally. Hypoplastic middle phalanx of little fingers. Ossification out of sequence at age 6 years. Flattened, sclerosed, fragmented, femoral heads and widened femoral necks. Skull normal.
18	+			147	16					+	67			
19	+									+				Ossification consistent with age. Fusion of hamate and capitate. 13 pairs of ribs. Dorsal kyphosis. Skull and chest normal. Barium swallow showed pyloric holdup, regurgitation into esophagus and high position of cecum.

TABLE IV.—LABORATORY AND X-RAY FINDINGS IN THREE CASES OF TYPUS DEGENERATIVUS AMSTELODAMENSIS REPORTED BY DE LANGE FROM AMSTERDAM AND IN 20 CASES REPORTED FROM BIRMINGHAM—*Continued*

Subject	*Normal chromosomes*	*Normal urine amino acids*	*P.B.I. (μg./100 ml.)*	*Cholesterol (mg. %)*	*Blood urea (mg. %)*	*Normal electrolytes*	*Ca (mg. %)*	*Pi (mg. %)*	*Fasting blood sugar (mg. %)*	*Abnormal E.E.G.*	*I.Q.*	*Abnormal E.C.G.*	*Findings on other investigations*	*X-ray abnormalities*
20	+	+	6.1	168	61	+	9.5	5.2	58	N.	43	N.	Normal growth hormone levels. Normal urinary 17 O.H.C.S. and 17 K.S. at age of 10 yrs. Normal plasma proteins	Bilateral short 4th metatarsals. Bilateral short 1st metacarpals. Bilateral short 5th metacarpals. Abnormal shape of middle and distal phalanges of little fingers. Fusion of several carpal bones (see case report). Unusual modelling at lower end of radius and ulna. Ossification consistent with age. Small skull with normal sella. Minor irregularities of shape of ribs and clavicles. Six lumbar vertebrae. Narrow thoracic vertebrae. Scoliosis.

A1, A2 and A3 represent W.G., P. de G. and G.P., the three cases described by de Lange.

erupt late, may be overcrowded or small and peg-like. Microcephaly is usual and plagiocephaly or brachycephaly common. The ears are usually low-set, and the neck often short or webbed. Hypertrichosis is usual and is particularly evident on the nape of the neck, back and forearms. The hairline is low posteriorly. The hands are usually small with short tapering fingers, a short incurved little finger, and a proximally placed thumb with a small thenar eminence. A single transverse palmar crease with high palmar triradiate creases, as in mongolism, is common. Syndactyly and gross deformities, including oligodactyly, micromelia and phocomelia, may occur. The feet are small. The toes are short and may be abnormally shaped; syndactyly of the second and third toes is common. Abnormalities of joints (particularly limitation of movement at the elbow joint with impairment of supination) are common. The skin is dry and rough with poor turgor; cutis marmorata may occur. Congenital heart disease, usually ventricular septal defect, may occur, and an increased incidence of gastrointestinal anomalies is reported. In the male the testes usually fail to descend and hypospadias may be present.

In infancy, the cry is low-pitched, growling and weak; in older patients a speech defect is very marked. Less significant findings which have been reported include deafness, bifid uvula, strabismus, nystagmus, coloboma, eccentric pupils, optic atrophy, capillary and cavernous hemangiomata, pigmented nevi, funnel chest, kyphoscoliosis, spina bifida occulta and malformations of the urinary tract.

The diagnosis is made from the history and physical examination. There are no definitive laboratory aids to confirm the diagnosis apart from a normal karyotype (exceptions will be discussed later). Schlesinger *et al.*[3] investigated the endocrine status in four patients and found evidence of defective function of the anterior pituitary. Hypogammaglobulinemia has been reported in several young patients.[4] An elevated blood urea is frequent without any evident cause.

Radiological studies have shown a number of deformities, the most consistent of which are a small or deformed skull, delayed ossifications, short metacarpals (particularly the first), short metatarsals, short phalanges, carpal bone abnormalities and posterior subluxation of the radius at the elbow joint.

A postmortem examination was done in nine cases. de Lange[2] reported subarachnoid hemorrhage, multiple sinus thrombosis, and nonfixation of the duodenum and descending colon. The brain weighed 1100 g. and an extensive subarachnoid hemorrhage was present. There was no gross abnormality on section. The surface showed an unusual pattern making it difficult to identify the fissure of Rolando, and convolutions were reduced in number. No very distinctive abnormalities were seen by microscope. Richter[5] reported a ventricular septal defect, patent ductus arteriosus, patent foramen ovale, purulent hemorrhagic pneumonitis and widespread hemorrhages of the adrenals, kidneys, liver and bladder mucosa. Schlesinger *et al.*,[3] two of whose cases were autopsied, reported brachycephaly of the skull, microcephaly, abnormal sella turcica, narrow cerebral convolutions, wide intergyral sulci, cortical atrophy, gliosis, degeneration of myelin, absence of basophilic cells in the pituitary, and hypoplasia of the thyroid, adrenals and the testicles. One case showed non-rotation of large and small gut and cortical nephrocalcinosis, and the other case had a duplication of the colon. Ptacek *et al.*[4] reported gross retarded development of all major organs except the liver. Hart, Jaslow and Gomez[6] reported microcephaly, an abnormal sulcal pattern

and wide gyri with reduction in cortical ganglion cells, small pituitary, thyroid and adrenal glands, abnormal lobation of the lungs, and non-rotation of the cecum with obstruction due to a fibrous band. Gans and Thurston[7] reported three autopsies: the first showed malrotation of the intestines and a hypoplastic thymus; the second showed an atrial septal defect, hypoplasia of the aorta and the aortic valve, a small non-functioning left ventricle, patent ductus, persistent left superior vena cava entering the right auricle, polycystic kidneys, and adrenals which joined in front of the aorta; and the third showed a ventricular septal defect, endocardial fibroelastosis of the right ventricle, a patent foramen ovale, hypertrophy of the circular muscle of the stomach and esophagus and multiple cysts in the outer zone of the renal cortex.

TABLE V.—de LANGE SYNDROME; REVIEW OF THE LITERATURE

Author and year	*Country*	*No. of cases*
de Lange, 1933	Netherlands	2
Vedder, 1935	Netherlands	1
de Lange, 1938	Netherlands	1
Pincherle, 1939	Italy	1
Marie *et al.*, 1946	France	1
Willemin-Clog *et al.*, 1947	France	1
Keizer, 1952	Netherlands	1
Arnaud-Battandier and Gillot, 1953	Algiers	1
Borghi *et al.*, 1954	Italy	1
Bardier and Degoy, 1956	France	1
Zunin, 1957	Switzerland	1
Zweymuller, 1957	Austria	1
Altozano, 1961	Spain	1
Richter, 1961	Germany	3
Giraud, 1963	France	1
Laurence and Ishmael, 1963	Great Britain	2
Schlesinger *et al.*, 1963	Great Britain	6
Hienz, 1963	Germany	1
Jervis and Stimson, 1963	United States	5
Ptacek *et al.*, 1963	United States	9
Geudeke *et al.*, 1963	Netherlands	3
Noe, 1964	United States	4
Silver, 1964	United States	1
Bishun, 1965	Great Britain	1
Hart, 1965	United States	6
Smithells, 1965	Great Britain	2
Dodge, 1965	Northern Ireland	1
Aberfield, 1965	United States	2
Gans, 1965	Great Britain	4
Falek, 1966	United States	4
Total		69

Familial cases are unusual. The full syndrome is easily recognized but must be differentiated from Hurler's syndrome, Turner's syndrome, cretinism, Rubinstein and Taybi syndrome and from generalized abnormalities related either to apparent or concealed chromosomal imbalance. The syndrome described by Rubinstein and Taybi,[8] which is readily confused, has a characteristic face, and broad thumbs and broad big toes. In the neonate, trisomy 18 may be suggested on superficial examination.

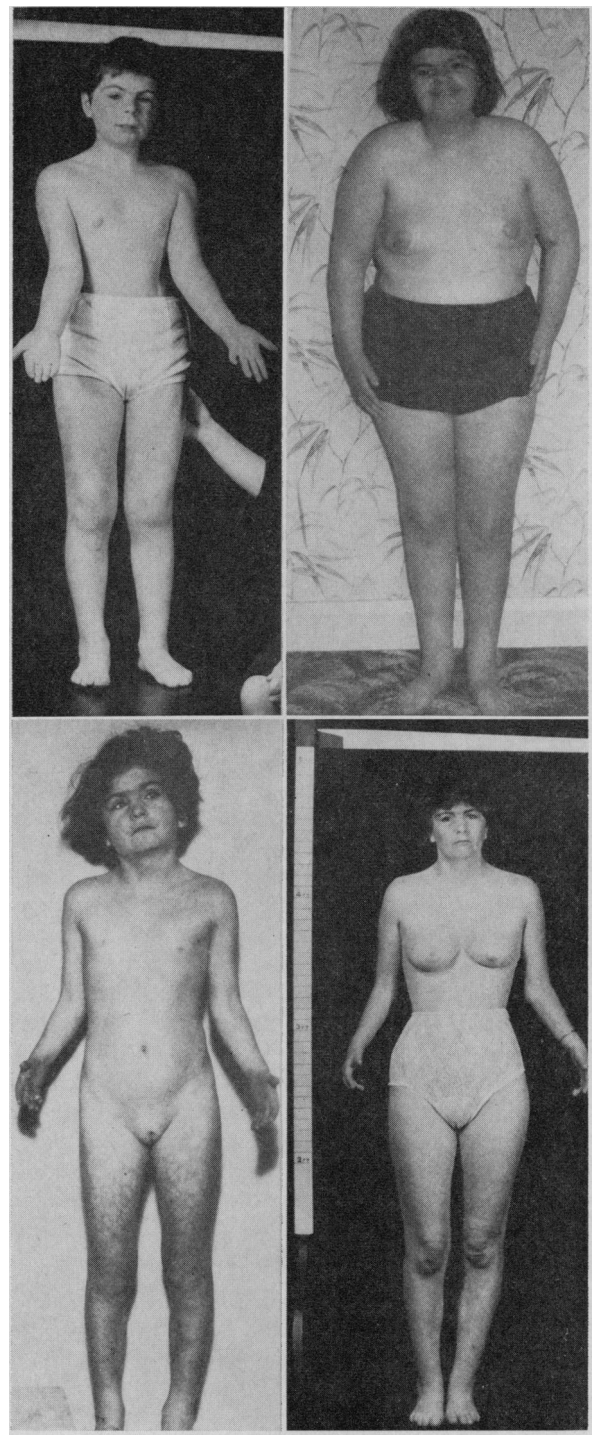


Fig. 4.—Appearance of older cases: top left, Case 17, aged 10 years: top right, case 19, aged 14 years; bottom left, Case 21, aged 10 years; bottom right, Case 20, aged 17 years.

Sixty-nine cases of Typus Degenerativus Amstelodamensis (de Lange syndrome) have been reported in the literature (Table V). In this paper we present 20 additional cases. All were

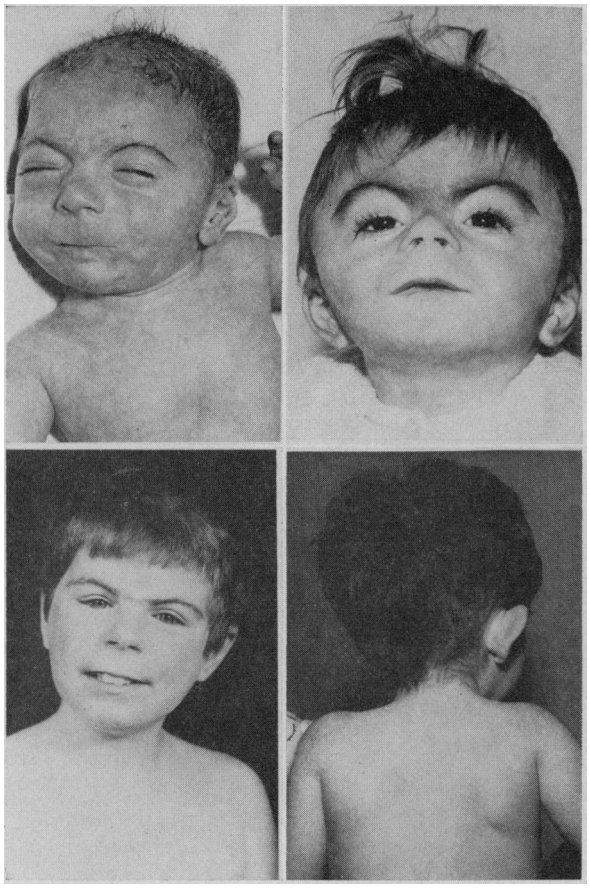


Fig. 5.—Typical face and hypertrichosis: top left, Case 2, at age 4 months; top right, Case 6, at age 9 months; bottom left, Case 17, at age 10 years; bottom right, Case 8, at age 2 years.

referred to one of us as conditions in which it was thought that chromosomal analysis might be of value or interest. A minority had already been diagnosed as cases of de Lange syndrome.

Case Reports

The symptoms, signs, and laboratory and radiographic findings in de Lange's three cases and our 20 cases are tabulated in Tables I to IV.

There was no history or evidence of familial incidence, significant family illness, exposure to drugs during pregnancy, advanced maternal age, sex predominance or consanguinity. Gestation ranged from 35 weeks to 41 weeks with 16 of the cases being at least 38 weeks' gestation. Eleven infants weighed less than 3.3 kg. at birth, eight of these being less than 2.5 kg. Although premature birth was frequent, there was no gross disturbance in fetal growth rate. The parental age distribution was unremarkable; the average maternal and paternal ages were 28.3 and 29.9 years, respectively. Cyanosis, apnea, hypertonia, difficult feeding, vomiting, recurrent infections (particularly chest), a low-pitched growling cry and delayed milestones were usually present. Although mental retardation was evident in all our cases, the major retardation was that of speech. Speech was far more retarded than comprehension and learning. Feeding difficulties, recurrent infections and hypertonia usually improved after the age of 2 years. However, one patient (Case 20) was unable to tolerate solid foods until age 12. Most patients had proper bowel and bladder habits by the age of 5 years, although enuresis has persisted in the two eldest patients (Cases 19 and 20), aged 14 and 18 years.

All cases showed major signs of mental retardation, typical face, characteristic deformities of arms, hands and feet, hypertrichosis (which decreased with age). The majority had microcephaly and growth failure, which in this syndrome need not be marked, but the latter, a common feature in the young child, may not be so evident in the older patient. The typical appearance of these children is shown in Figs. 2, 4, 5 and 6. The growth development of Cases 19 and 20 is plotted graphically in Figs. 7 and 8. Case 19, after falling below the third centile in the first year of life after a reported normal birth length, did not attain the third centile for height until 8 years of age. Case 20 was well below the third centile until the age of 12 years, when a definite growth spurt became evident. She is now 18 years of age and her height is 151 cm., just below the third centile. Of the 11 males in the series, eight had undescended testes and two of these had hypospadias. The eldest boy was 11. All girls over the age of 10 (Cases 16, 17, 19 and 20) showed normal secondary sexual development, and both girls over the age of 14 were menstruating.

Abnormalities of the joints, ranging from limitation of movement at the elbow joint with impairment of supination to generalized flexion deformities, were present in 10 patients; cutis marmorata and vascular lability were present in 10; eight had a funnel chest and eight had squint. Four had cleft palate and 10 a very narrow, high-arched palate. Pyloric stenosis was confirmed at surgery in one. The small, peg-like teeth reported in young patients were not always present; the older children, in particular, often had large, irregular, overcrowded teeth.

The colouring of our patients was remarkable, the majority being dark-haired, often black-haired, although there was no evident tendency to darkness of the skin or eyes. Some of this dark colouration was doubtless due to selection. Most patients were referred for chromosome studies without a diagnosis, but even in this group the dark hair and eyebrows tended to distort the

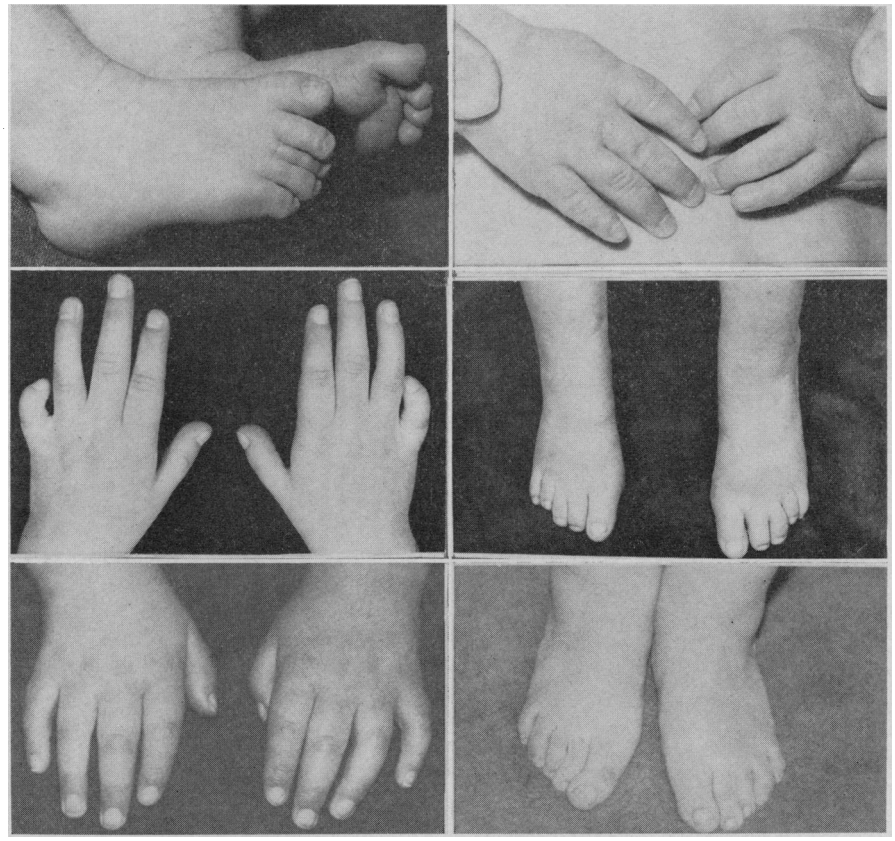


Fig. 6.—Typical hands and feet: top, Case 6, age 9 months; middle, Case 20 at age 18 years; bottom, left to right, Case 18 at age 11 years and Case 19 at age 14 years.

facial appearance and suggested a generalized disorder. However, we consider this an inadequate explanation, and since it is unlikely that such a distinct generalized syndrome should be commoner in dark-haired children, we must suppose that a disturbance of hair pigmentation is a distinct part of this syndrome. Since it is the most consistent biochemical anomaly, detailed study of it might be well worth while.

The results of cases investigated at various hospitals are tabulated in Table IV. (Five of these had radiological examinations done at Birmingham Children's Hospital and were reported to us by Dr. R. Astley.)

General findings in patients with de Lange's syndrome include short first metacarpals, which may be abnormally shaped. The fingers may have deformed phalanges, especially the middle phalanges, with incurving. Some of the carpal bones may be fused. The feet may be short; shortening of one or more of the metatarsals may be present. Proximal syndactyly of the soft tissues may be seen. The skull may be small, with a rather prominent facial region. Unerupted teeth may be seen.

The spine may show scoliosis, small sacral wings, and narrow vertebral bodies. Two patients showed six lumbar vertebrae. Minor abnormalities in shape were present in many bones, particularly the clavicles, ribs and at the elbow and wrist. The trabecular pattern of bones tended to be coarse. An 11-year-old girl of slight build (Case 17) had bilateral Perthe's disease.

The oldest three girls, 11, 14 and 18 years of age (Cases 17, 19 and 20), showed normal bone age although in one, radiographs at the age of 7 had shown gross growth retardation (Fig. 9).

Chromosome studies were carried out in every patient and were normal. Eighteen patients were studied by lymphocyte culture alone. Case 19 was studied by Dr. Marco Fraccaro on a fibroblast culture derived from a skin biopsy. Case 20, which was studied by Dr. C. E. Ford on short-term marrow culture and on fibroblast cultures established from three sites, was the patient most intensively investigated. In Case 17, repeated lymphocyte cultures provided cells of exceptionally high quality from the child and both parents, but no anomaly was evident on direct visual analysis by four experienced observers. These three patients demonstrated the most typical cases of de Lange's syndrome in our series. Normal urine amino acid values, examined

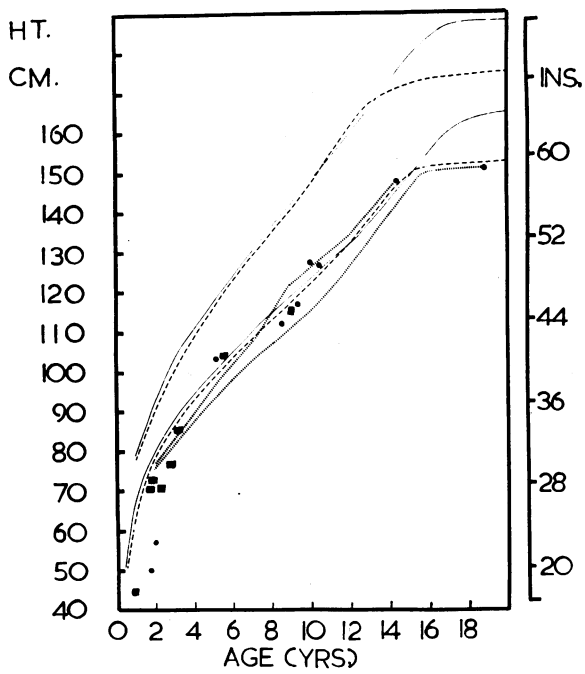


Fig. 7.—Height against age. Solid black line represents the third and 97th centile for boys. Interrupted black line represents the third and 97th centile for girls. The dotted black line represents the linear growth of Cases 19 and 20 respectively. The heights of 17 patients at the time of investigation are shown; squares represent boys, circles represent girls. Cases 1, 10 and 18 are not plotted.

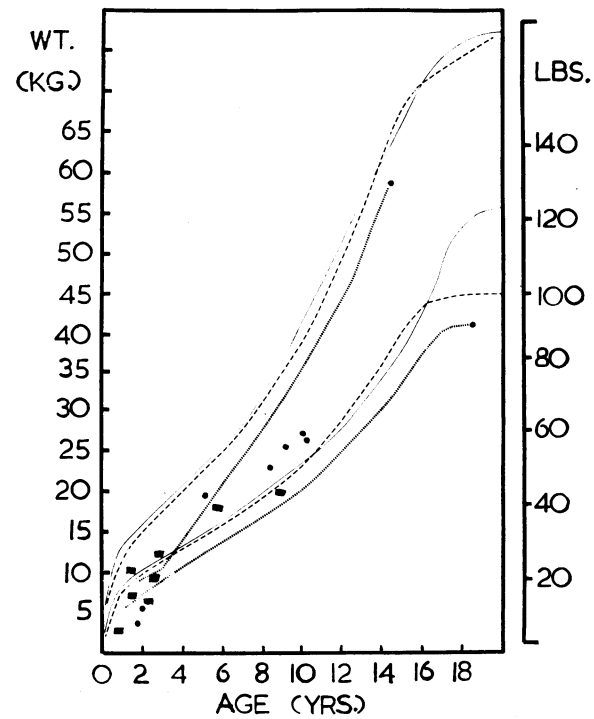


Fig. 8.—Weight against age. Solid black line represents the third and 97th centile for boys. Interrupted black line represents the third and 97th centile for girls. The dotted black line represents the weight growth of Cases 19 and 20 respectively. The weights of 17 patients at the time of investigation are shown; squares represent boys, circles represent girls. Cases 1, 10 and 18 are not plotted.

by paper chromatography, were reported in six patients. Serum protein bound iodine determinations were done on four patients and were within the normal range; one was borderline. Serum cholesterol was estimated in eight subjects; three of these had values above 200 mg. Of four patients having elevated blood urea nitrogen levels, two had chronic urinary tract infections and in the remainder no cause was found. Serum electrolytes, calcium and phosphorus, and fasting blood sugar were normal in all those studied. Case 20 manifested normal values for 24-hour urinary excretion of 17-hydroxycorticosteroids and 17-ketosteroids. The fasting plasma growth hormone (radioimmune technique of Hartog *et al.*[10]), in this patient was 37 ng./ml., well above the lower limit of normal. Case 3 also had a fasting growth hormone level greater than 10 ng./ml.

Electroencephalograms (EEG) were done in five patients. Three of the five had abnormal EEG patterns, the patterns being dissimilar. Con-

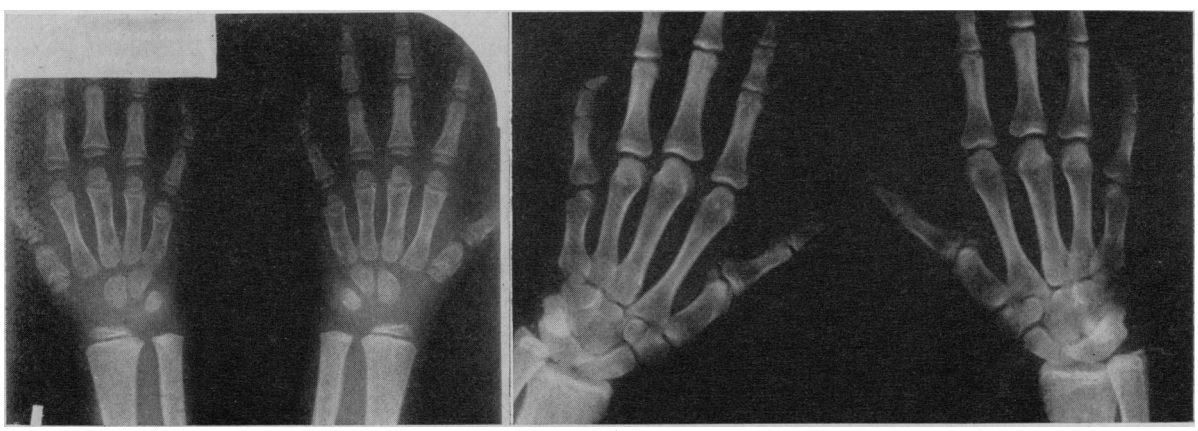


Fig. 9.—Radiographs of carpal bones of Case 20 at age 7 and 18 years. Bone age grossly retarded at age 7 and normal at 18. Also at age 18 note fusion between trapezium and trapezoid, capitate and hamate and between triquetral and lunate.

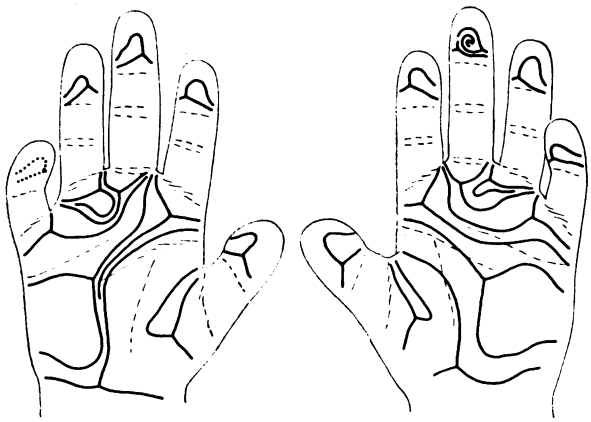


Fig. 10.—Palm prints of Case 20. (Drawn by Christine Blowfield.)

vulsions were present in two of these three patients, and these convulsions were also dissimilar. It seems possible that the etiology may be developmental, or acquired at birth as the result of trauma and anoxia. Assessment of the intelligence quotient varied from 20 to 67; other tests revealed a disproportionate speech deficit.

Demonstrable gastrointestinal abnormalities, typical of the increased incidence of alimentary pathology in de Lange syndrome, were present in three patients.

Palm prints of the eldest patient (Case 20) are shown in Fig. 10.

Pathological Studies

On only one of our patients was an autopsy performed (Case 2, whose age at death was 9 months). Because of the rarity of detailed reports about undoubted cases with normal chromosomes, it is presented in detail. The autopsy was carried out by Dr. A. H. Cameron and examination of the brain by Professor E. Guli.

The external appearance of this patient is illustrated in Fig. 2. Bilateral cleft palate involving the posterior two-thirds of the hard palate and all of the soft palate was present. No other cause for dysphagia was found. There was abnormal lobation of the lungs, both lower lobes showing a fissure partly dividing the upper part of the lobe from the remainder. The posterior parts of both lungs were deeply congested and firmer than normal. The heart and great vessels were normal. The abdominal cavity showed a small Meckel's diverticulum, and the mesentery of the bowel was not fixed anywhere. The ileocecal bowel lay in the epigastrium. The testes were of normal size and both lay close to the internal rings in the abdominal cavity. The abdomen and its contents were otherwise normal. There was no abnormality of the middle ears, venous sinuses or meninges. The brain was below

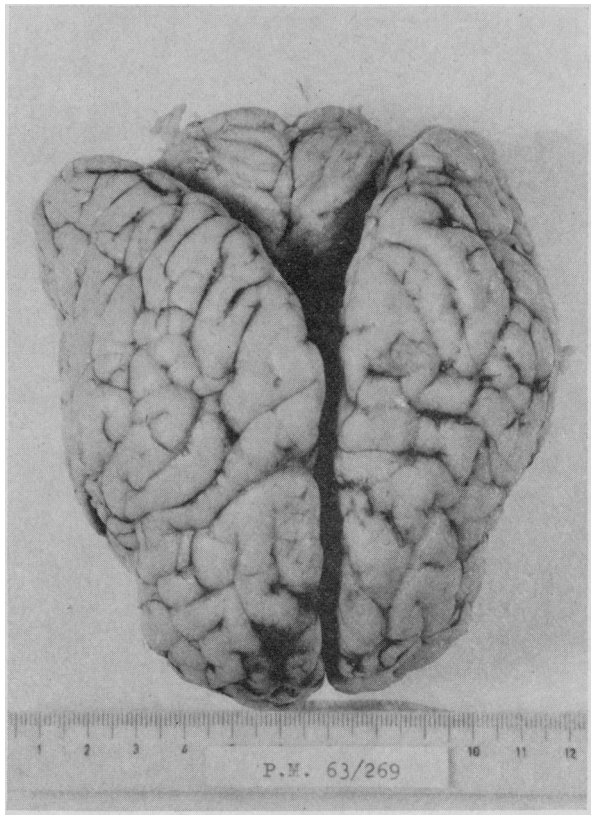


Fig. 11.—Brain, Case 2, aged 9 months. Small cerebral hemispheres but normal gyri.

its expected weight and the cerebral hemispheres were smaller than normal. The gyri were of normal thickness and showed an apparently normal pattern (Fig. 11). The cerebellum was not reduced in size. No specific microscopic lesions were detected. The posterior clinoid process was longer than normal and overhung the pituitary fossa. The fossa itself was of normal size. The pituitary gland was normal, its maximum transverse diameter being 0.85 cm. Microscopic examination showed the distribution of cells in the pituitary to be normal, and there was no reduction in eosinophils or basophils; most of the latter were of the intermediate paler variety. The thyroid was one-third the average size for this age. The adrenals were normal and contained a considerable amount of lipid. Sectioning of the vertebral column showed no abnormalities of the vertebral bodies and normal marrow.

Organ weights (related to body length) were: brain, 442 g., normal 489 g.; lungs, left 41 g., right 40 g., normal 30 g. each; heart, 32 g., normal 23 g.; thymus, 7 g., normal 20 g.; liver, 165 g., normal 136 g.; spleen, 19 g., normal 13 g.; adrenals, left 1.5 g., right 1.10 g., normal 5 g. together; and kidneys, left 20 g., right 19 g., normal 19 g. each.

Discussion

The etiology of the condition remains obscure. It is clearly a distinct syndrome manifest at

birth and affecting some structures, such as the limb ends, which are formed in early fetal life. The consistency of the manifestations, the presence of abnormalities in early fetal life, and the very generalized nature of these abnormalities affecting almost every tissue, are strongly suggestive of a genetic disorder.

A recessively determined disorder is, in our opinion, excluded by the rarity of familial cases and by the fact that the majority of reported cases are sporadic, in spite of selection favouring both the recognition and reporting of familial cases. However, Opitz *et al.*[11] refer to five sibships with 14 affected cases, and consider recessive inheritance likely. A point mutation manifest in the heterozygote, although formally possible, is unlikely, since the incidence, which is probably at least one in 10,000 births, exceeds any likely mutation rate. In addition there is no parental age effect.

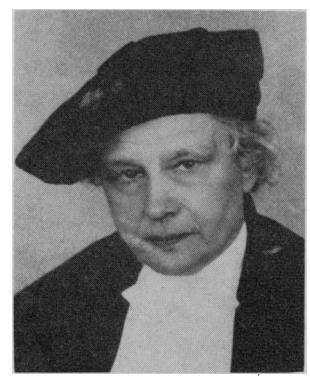
A chromosomal origin seems likely, and many cases have been examined. In none of our cases was any anomaly detected, although all were examined and several of the more typical cases were examined in great detail by several observers. The examinations were of well-prepared specimens. Such examinations, while excluding any marked anomaly, cannot exclude small deficiencies. The disturbance from deficiency of the short arm of a No. 18 chromosome is almost as severe as this, and the absence of a fragment of this magnitude from a long chromosome arm would not be detectable. A small duplication, although unlikely to produce such a marked phenotypic disturbance as a deficiency of equivalent length, might also escape detection.

One series of familial cases has been recorded[12] in association with a translocation between chromosomes 3 and 21 or 22. The unbalanced cases apparently are related to an additional segment from one end of a number 3 chromosome, and assuming the translocation was reciprocal, a small deficiency in the small arms of No. 21 or 22.

It seems unlikely that this small deficiency would have any marked effect, since such deficiencies are common in the parents of various types of translocation mongols and usually without effect. Ford[13] studied a biopsy from a patient referred from Amsterdam by van Creveld and found an apparently balanced rearrangement involving chromosomes.[4, 5, 13, 14] He suggested that a related deficiency was likely to be the cause of the condition. Other reports on abnormal chromosomes in this syndrome have been published,[14] but are not wholly satisfactory on technical grounds.

It seems to us most likely that the condition is related to a chromosomal deficiency which is not usually detectable, although it may be associated with evident translocations involving larger pieces of chromosome. This will explain both the usually sporadic nature of the condition and its occasional familial concentration, since the deficiency may arise *de novo*, or may be latent in the form of a balanced rearrangement in a parent.

A defect in this hypothesis is that the chromosomes reported to be involved are different in the two observations in which the diagnostic and cytological standards seem completely acceptable. Further, in the case described by Falek, Schmidt and Jervis[12] a duplication anomaly was evidently present and the related deficiency was in an apparently inert region. We must either infer that their case demonstrated a duplication anomaly of part of a third chromosome as the causal factor, the effective part of this duplication being a very small terminal segment of the third chromosome, or infer that it was a close mimic of this syndrome, or that the chromosomal rearrangement was even more complex than the recognizable abnormalities implied.



Dr. Cornelia de Lange.

If either of these latter explanations is correct, we could relate the deficiency to the long arm of either a (4, 5) or a (13-15) on the evidence of the case quoted by Ford.[13] It seems to us even more unlikely that both chromosomal rearrangements were irrelevant to the phenotype, or that in neither was the syndrome correctly diagnosed.

However, it is difficult to diagnose generalized syndromes accurately without experience, which cannot be readily acquired in such rare diseases. An experience of at least a dozen cases of mongolism or of either of the two other trisomic syndromes is necessary before precise clinical diagnosis is possible, and we have no reason

to assume that the diagnosis of de Lange syndrome is any easier. Indeed, the recognition of this syndrome is one of the most remarkable feats of clinical taxonomy, and one of the few to deserve eponymity.

We have no doubt that many of the published cases, including several of our own, are misdiagnosed. These others closely resemble this distinct and genuine syndrome which, we suspect, may be simulated by many other generalized disorders, particularly those related to chromosome imbalance, with or without evident reciprocal translocations.

Our present understanding of this condition can be summarized by the last paragraph of de Lange's second paper. The original is given in the appendix.

"Can we say then that these anatomical findings represent the 'typus Amstelodamensis'? We are still far from that. Now that the condition can be recognized, autopsies on further cases can give us more information. Since most of these children will spend some part or other of their life in a home for backward children, it is there we must look for them. Even so the type appears to be somewhat rare. Until now these observations have been presented as isolated cases. We have not noticed similar cases in numerous children of the same parentage or same generation."

SUMMARY

Twenty cases of de Lange syndrome are presented. The chromosomes appeared normal in all affected patients. The clinical findings are presented, and one autopsy is reported. The literature is briefly reviewed.

We would like to thank Dr. Roy Astley, Dr. A. H. Cameron and Dr. E. Guli for reporting on the radiological, pathological, and neuropathological findings, and Dr. C. E. Ford and Dr. Marco Fraccaro for undertaking chromosome examinations on two patients; to Mrs. Tessa Dent for many of the chromosome analyses, and Dr. G. W. Aldridge, Dr. Margaret Barton, Dr. B. D. Bower, Dr. D. W. Bull, Mr. W. Butt, Dr. W. H. P. Cant, the late Dr. I. H. Gossett, Dr. Eileen Hill, Professor D. V. Hubble, Dr. Margaret Noble, Dr. C. Ounstead, Dr. Parry-Williams, Dr. Victoria Smallpiece and Dr. S. B. Wood. We are indebted to Miss Judith Cook and her department who did much of the photography.

We are also indebted to Professor Tegelaers of Amsterdam for lending photographs of Professor de Lange and of her original cases, and to him and to Professor Derom of Ghent for providing and translating biographical data.

One of us (J.H.E.) is greatly indebted to the late Dr. I. H. Gossett and Dr. Ounstead for drawing our attention to this condition and encouraging its chromosomal investigation in 1959.

APPENDIX

1. de Lange, C.: Sur un type nouveau de dégénération (Typus Amstelodamensis). *Arch. Méd. Enf.*, 36: 713, 1933.

"Quels sont maintenant les traits obligatoires de cette dégénération combinée (multiple Abartung), quels les traits accidentels? Pour se former une opinion sur cette question il sera nécessaire d'analyser un plus grand nombre de cas. Pourtant, il me semble probable que la débilité mentale, le chétivisme (naissance à terme avec poids inférieur qui reste bien au dessous de la moyenne), la brachycéphalie, les sourcils et les cils hypertrophiés, la petitesse des mains et des pieds, la position proximale du pouce et de l'éminence thenar, la position basse des oreilles, la syndactylie des orteils soient des symptômes obligatoires. L'hirsutisme du front, la voute palatine ogivale, le petit doigt en crochet ainsi que la micromélie humérale se rangent peut-être parmi les symptômes accidentels. La syndactylie n'affecte évidemment pas toujours les mêmes orteils."

2. de Lange, C.: Nouvelle observation du "Typus Amstelodamensis" et examen anatomopathologique de ce type. *Arch. Méd. Enf.*, 41: 193, 1938.

"Peut-on dire maintenant que cas donnés présentent le substratum anatomo-pathologique du typus Amstelodamensis? Nous sommes encore loin de cela. Maintenant que le type est connu, de nouvelles observations avec autopsie doivent nous instruire sous ce rapport. Comme la plupart de ces enfants, au cours d'une période quelconque de leur vie, seront probablement internes dans un asile pour enfants arrières, c'est là qu'il faut chercher. Le type pourtant semble être assez rare. Jusqu'ici, les observations se sont présentées comme des cas isolés; on n'a pas observé de tels cas chez plusieurs enfants des mêmes parents ou de la même génération."

REFERENCES

1. DE LANGE, C.: *Arch. Méd. Enf.*, **36**: 713, 1933.
2. *Idem*: *Ibid.*, **41**: 193, 1938.
3. SCHLESINGER, B. *et al.*: *Arch. Dis. Child.*, **38**: 349, 1963.
4. PTACEK, L. J. *et al.*: *J. Pediat.*, **63**: 1000, 1963.
5. RICHTER, H.: *Arch. Kinderheilk.*, **164**: 249, 1961.
6. HART, Z. H., JASLOW, R. I. AND GOMEZ, M. R.: *Amer. J. Dis. Child.*, **109**: 325, 1965.
7. GANS, B. AND THURSTON, J. G. B.: *Develop. Med. Child Neurol.*, **7**: 42, 1965.
8. RUBINSTEIN, J. H. AND TAYBI, H.: *Amer. J. Dis. Child.*, **105**: 588, 1963.
9. BRACHMANN, W.: *Jb. Kinderheilk.*, **84**: 225, 1916.
10. HARTOG, M. *et al.*: *Brit. Med. J.*, **2**: 1229, 1964.
11. OPITZ, J. M. *et al.*: *Lancet*, **2**: 1019, 1964.
12. FALEK, A., SCHMIDT, R. AND JERVIS, G. A.: *Pediatrics*, **37**: 92, 1966.
13. FORD, C. E.: Autosomal abnormalities. *In*: Second International Conference on Congenital Malformations, New York, 1963. Papers and discussions, compiled and edited by the International Medical Congress, New York, 1964, p.
14. JERVIS, G. A. AND STIMSON, C. W.: *J. Pediat.*, **63**: 634, 1963.